

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

26 APR 2005



Applicant's or agent's file reference X-16024	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA416)	
International application No. PCT/US 03/31514	International filing date (<i>day/month/year</i>) 24.10.2003	Priority date (<i>day/month/year</i>) 05.11.2002
International Patent Classification (IPC) or both national classification and IPC C07C217/64		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☒ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 29.04.2004	Date of completion of this report 04.04.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Österle, C Telephone No. +49 89 2399-8120 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 03/1514

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, Pages

1-95 as originally filed

Claims, Numbers

1-15, 23-52 as originally filed

16-22 filed with telefax on 10.12.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - ☐ the entire international application,
 - ☒ claims Nos. 1-15 (in part), 18-25, 32-38 and 39-52 (in part)
because:
 - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☒ no international search report has been established for the said claims Nos. 1-15 (in part), 18-25, 32-38 and 39-52 (in part)
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - ☐ the written form has not been furnished or does not comply with the Standard.
 - ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:
 - ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☐ not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

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- ☒ all parts.
☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-15 (in part), 16-17,26-31 and 39-52 (in part)
	No: Claims	
Inventive step (IS)	Yes: Claims	1-15 (in part), 16-17,26-31 and 39-52 (in part).
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-48
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 49-52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
2. Claims or parts of claims relating to compounds for which Y is not unsubstituted or substituted phenyl or benzothienyl have not been subject to search. Parts of the claims for which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). No opinion with regard to novelty and inventive step therefore has been established for subject-matter of claims 1-15 (in part), 18-25, 32-38 and 39-52 (in part).

Re Item IV

Lack of unity of invention

In order to satisfy the requirement of unity compounds cover by a Markush-formula must have a significant structural element in common. Furthermore, this common part of the structure must distinguish the compounds from any known compounds having the same property/activity.

The structural element common to all compounds of present claim 1 is the skeleton C-C-CH-CH-CH₂-NR₁R₂.

This structural element is however known for compounds of the prior art having the same activity (see EP 0373836, wherein R¹ is phenyl or C₅-C₇ cycloalkyl (see also examples) and US 5,023,269, wherein R¹ is C₅-C₇ cycloalkyl (see also examples in columns 3 and 4)).

Present claim 1 therefore lacks unity (Rule 13.1 PCT).

The following groups of inventions therefore are not so linked as to form a single general inventive concept:

1. compounds wherein X=C₂-C₆ alkyl (claims 1-8 (part), 9-11 and 16-52 (part))

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2. compounds wherein X=C2-C8 alkenyl (claims 1-8 (part), 12,13 and 16-52 (part))
3. compounds wherein X=C3-C8 cycloalkyl (claims 1-8 (part), 14,15 and 16-52 (part))
4. compounds wherein X=C4-C8 cycloalkylalkyl (claims 1-8 (part) and 16-52 (part))

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: T.L. LEMKE: "beta-Adrenergic blocking agents. alpha- and gamma-Methyl(aryloxy)propanolamines" J.MED.CHEM., vol. 24, no. 10, 1981, pages 1211-1214, XP002275394
- D2: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 30 November 1988 (1988-11-30), XP002275395
Database accession no. BRN: 1463192 AND 1468893
- D3: EP-A-0 373 836 (LILLY CO ELI) 20 June 1990 (1990-06-20)
- D4: US-A-5 776 969 (JAMES STEVEN PARKER) 7 July 1998 (1998-07-07)
- D5: US-A-5 023 269 (ROBERTSON DAVID W ET AL) 11 June 1991 (1991-06-11)
- D6: WO 02/094262 A (RATHMELL RICHARD EDMUND ; FAGAN MARIA ANN (GB); GALLAGHER PETER THADDE) 28 November 2002 (2002-11-28)

1. Novelty (Article 33(2) PCT):

- 1.1 D1 and D2 differ from the compounds of formula I of claim 1 in that the substituent X in claim 1 comprises at least two carbon atoms.
- 1.2 D3 (EP 0 373 836) discloses serotonin and norepinephrine uptake inhibitors of formula (I). Formula (I) of D3 and formula (I) of claim 1 have a broad area of overlap for A=S, Z=H, Y=phenyl or naphthyl and X=cycloalkyl. The compounds of formula (I) of D3 however fall within the area defined by the proviso of claim 1. However, since

the compounds of D3 have the same activity as the presently claimed compounds, D3 is still relevant for the assessment of inventive activity.

The compounds of D3 differ from the compounds of the present invention in that in claim 1 Z=OH or OALK or F when Y=Ph or naphthyl.

1.3 D4 (US 5,776,969) discloses serotonin 1A receptor antagonists.

The compounds of D4 differ from the compounds of the present invention in that in claim 1 X is not =H.

1.4 D5 (US 5,023,269) discloses serotonin and norepinephrine uptake inhibitors. The compounds of D5 and the compounds of formula (I) of claim 1 have a broad area of overlap for A=O, Z=H and X=cycloalkyl. The compounds of formula (I) of D5 however fall within the area defined by the proviso of claim 1. However, since the compounds of D5 have the same activity as the presently claimed compounds, D5 is still relevant for the assessment of inventive activity.

The compounds of D5 differ from the compounds of the present invention in that in claim 1 Z=OH or OALK or F when Y=Ph or naphthyl.

1.5 The subject-matter of claims 1-15 (in part), 16-17,26-31 and 39-52 (in part) then can be considered novel.

2. Inventive Activity (Article 33(3) PCT):

2.1 D3 or D5 can be considered the closest prior art since both documents disclose serotonin and norepinephrine uptake inhibitors which are structurally close to the compounds of the present invention.

The difference between D3 or D5 and the compounds of present claim 1 is that substituent Z of claim 1 is defined as OH or OALK or F when Y=Ph or naphthyl.

Since the compounds of the invention and the compounds of D3 or D5 have the same activity, the technical problem can be seen in providing further compounds which are serotonin and norepinephrine uptake inhibitors.

The solution suggested are the compounds of formula (I) of claim 1.

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From D3 or D5 it was not obvious to arrive at the presently claimed compounds. D4 discloses compounds for which $Z=OH$, however, these compounds have a different activity. A combination of D4 with D3 and/or D5 therefore cannot be considered obvious.

2.2 The subject-matter of claims 1-15 (in part), 16-17, 26-31 and 39-52 (in part) then can be considered inventive as well.

3. Industrial Applicability (Article 33(4) PCT):

The subject-matter of claims 1-48 is considered industrially applicable.

16. A compound as claimed in any one of the preceding claims, wherein Y is phenyl optionally substituted with up to 5 substituents each independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkyl-S-, -CF₃, and -SCF₃.

5 17. A compound as claimed in claim 16, wherein Y is phenyl optionally substituted with up to 2 substituents each independently selected from F, Cl, Br, I, Me, Et, OMe, SMe, -CF₃, and -SCF₃.

10 18. A compound as claimed in any one of claims 1-15, wherein Y is naphthyl optionally substituted with up to 5 substituents each independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkyl-S(O)_n- where n is 0, 1 or 2, nitro, acetyl, -CF₃, -SCF₃ and cyano.

15 19. A compound as claimed in claim 18, wherein Y is unsubstituted naphthyl or naphthyl which is mono-substituted with a substituent selected from halo, C₁-C₄ alkyl and -CF₃.

20 20. A compound as claimed in claim 19 wherein the substituent is located at the 4-position of the naphthyl ring.

21. A compound as claimed in any one of claims 18-20, wherein the point of attachment of the optionally substituted naphthyl group to the -O- or -S- atom is attachment at the 1 position.

25 22. A compound as claimed in any one of the claims 1-15, wherein Y is benzofuranyl, benzothiazolyl, benzoisothiazolyl or indolyl each of which may be optionally substituted with up to 4 or, where possible, 5 substituents each independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkyl-S(O)_n- where n is 0, 1 or 2, nitro, acetyl, -CF₃, -SCF₃ and cyano; and when Y is indolyl it may be substituted or further substituted by an
30 N-substituent selected from C₁-C₄ alkyl.